# Hay fever and the effect of influenza vaccines

**Authors**
TetsuroYamamoto[1]
Tadao Enomoto[2]
Muneaki Iizuka[1]
Hideyo Yamaguchi[1]
Shaw Watanabe[3]

**Affiliations**
[1]TTC Co. Ltd. Tokyo
[2]NPO Japan Health Promotion Supporting Network, Wakayama
[3]Lifescience Promoting Association, Kyoto

**Correspondence:**
Shaw Watanabe, M.D., Ph.D.
watashaw@lifescience.or.jp
tel +81-90-3095-1187
Address: 1-14-9, Nishi, Kunitachi-city, Tokyo 186-0005, Japan

**Abstract**
Hay fever is an increasing disease in Japan, and the prevalence of cedar pollinosis exceeds 20% nationwide. More than 50 kinds of pollen have been reported so far in Japan. Pollinosis often complicated other allergic conditions. Since patients with allergic diseases have lower s-IgA levels than healthy subjects, patients with hay fever have less weak mucosal immunity so that it would affect the efficacy of the influenza vaccine. Eight thousand three hundred thirty-seven (3885 men and 4452 women) participated in this survey to clarify the relationship between allergic diseases and the influenza vaccine's efficacy. In the no hay fever group, the effective vaccine rate against influenza disease was 0.2%, and in the hay fever group, it was 0.21%. No effect of the influenza vaccine was present in this population. Rather, vaccination seemed to increase influenza incidence in people with hay fever. The basic presence of allergic condition influenza vaccination increased susceptibility to influenza infection. (12.9% vs. 13.89%) ($p<0.001$). A tailor-made strategy for these patients should be necessary for preventing influenza.

**Key words:** Hay fever, pollinosis, allergic rhinitis, asthma, atopy, conjunctivitis, influenza, vaccine

## Introduction

The mucosal surface of nasopharyngeal region, bronchus, and digestive tract are about 200m$^2$, 200 times as wide as that of the skin. Epithelial cells covering mucosa are vulnerable and mucous membranes are sources of various diseases from the outside world.

About 95% of all infections are in the oral cavity, respiratory tract, digestive tract, conjunctiva, and genitourinary tract. The upper respiratory tract infections are one of the most common.

New coronavirus also passes through the upper respiratory tract.[1]

Hay fever is an increasing disease in Japan, and the prevalence of cedar pollinosis exceeds 20% nationwide. There are many kinds of pollen that cause pollen, and more than 50 types of pollen have been reported in Japan.[2] Most of the trees are Japanese cedar and cypress, but there are also birch, alder, zelkova, Quercus, beech, and rhododendron. In herbs, pollinosis of grasses such as Dactylis is common. Other examples are Asteraceae plants such as ragweed and mugwort. The central time of pollen dispersal is that the time when symptoms appear, is spring in trees such as cedar and cypress. Still, in the case of Poaceae, it is scattered in early summer, and in the case of Compositae, it is scattered from midsummer to autumn.

The Japanese cedar forest area occupies 18% of the forest and 12% of the national land. Therefore, about 70% of patients with hay fever are caused by cedar pollen. However, the amount of pollen varies from region to region, and the amount of cedar pollen scattered in Hokkaido is tiny, and cedar does not inhabit Okinawa at all. In the Kanto and Tokai regions, many cedar pollinosis patients are seen.[3]

When pollen enters from the nasal mucosa, the pili is carried out on the nasal mucosa to the outside of the nose. The pollen that remained and adhered to the mucous membrane and permeates the nasal mucosa with the antigen component.[4] There are mast cells in the mucous membrane of the nose, and in the case of cedar pollinosis patients, IgE antibodies against cedar pollen are bound around the mast cells. The IgE antibody captures and secures the cedar pollen's antigen that has melted, activates mast cells, and releases histamine. It stimulates nerves on the surface of the nasal mucosa, reflexively causing reflex secretion. Besides, histamine stimulates blood vessels, causing symptoms of stuffy. Also, in the conjunctiva, the IgE antibody on the mast cells and the cedar antigen component melted on the conjunctiva surface are bound to release histamine. Histamine also causes itching via nerves on the conjunctiva's surface, increases tear secretion in a reflexive manner and increases the sense of foreign body due to nerve hypersensitivity. Although cedar pollinosis has few general symptoms such as fever, many people complain of symptoms other than nose and eyes such as thirst, throat discomfort, and itchy skin.

The influenza vaccine has been found to have a certain degree of effect in suppressing onset, but it cannot be expected to have the high disease-preventing effect seen in the measles and rubella vaccines.[5-9] Most people recover from the illness within a week or so, but serious complications such as pneumonia and encephalopathy appear, and some require hospital treatment or die. There is a high possibility that the person who has an underlying disease or the elderly will become severe. [6] The most significant effect of the influenza vaccine is to prevent "severity."

Domestic research effectively prevented 34-55% of illnesses and 82% of mortality among the elderly who are 65 years or older in the welfare facility for the elderly. [8,9]

Since patients with allergic diseases have lower s-IgA levels than healthy subjects, it is thought that patients with hay fever have less weak mucosal immunity so that it would be a high risk of influenza virus infection. This study aims to clarify the relationship between hay fever and related allergic diseases and influenza incidence rate.

## Method

The subjects were recruited to participate in the ” hay fever and influenza study” from the registered clinical trial members. An invitation to the study was carried out by the internet site and enrolled those who had hay fever or other allergic diseases. Eight thousand three hundred thirty-seven people from about 200,000 registered people nationwide fulfilled the questionnaire. They were awarded for receiving 10 points for internet service.

Two specialists familiar with hay fever and influenza clinical trials made the questionnaire. [10,11] Questions included necessary information such as an address, name, sex, date of birth, height, weight, BMI, presence of hay fever, presence of allergic diseases, such as allergic rhinitis, asthma, atopy, presence or absence of allergic conjunctivitis, and medical history. Influenza incidence was asked from autumn 2006 to spring 2009 for three years and a history of vaccination from 2006 to 2009.

The data were stored in the Exell database and transferred to SPSS for statistical analysis. Influenza morbidity and vaccination for each year were summed up for a total of three years, and the influenza morbidity and effects of vaccination concerning the presence or absence of hay fever were analyzed.

The research was conducted in 2009 in the “Questionnaire Survey on History of Allergic Diseases and History of Influenza” approved by the TTC. (TTC21607)

The ethical aspect for the presentation of this paper was approved by the Ethics Committee of the Life Sciences Promoting Society (#2020-05)

## Result

There were 8337 participants (3885 men and 4452 women), who completed

the survey questionnaire. The average age and standard deviation were 43.4±10.6 years of age, and BMI was 22.9±3.9 Kg/m$^2$. The number of affected cases by region was almost the same as previous Japan.[8,9] The existing allergic disease was 3785 (45.7%) with hay fever, and 82.1% had an allergic disease. (Table 1) The prevalence of hay fever was low in Hokkaido and high in Kanto and Chubu, where cedar tree cultivation is widespread.

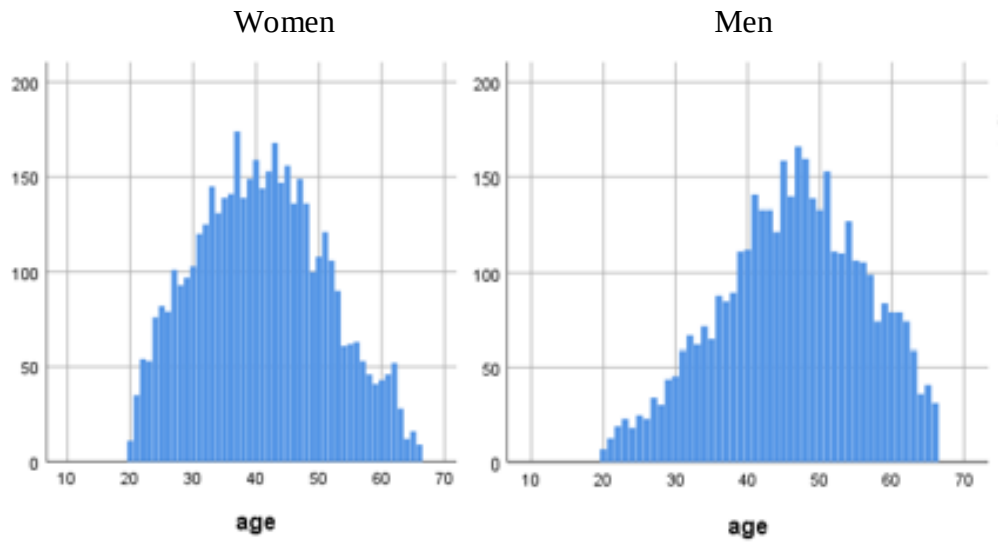


Fig. 1. Histogram of the age of participants by sex

Table 1. Districts of participants and kind of allergic diseases

| | total1 | heyfever | rhinitis | asthma | atopy | conjunctiv | total |
|---|---|---|---|---|---|---|---|
| Hokkaido | 348 | 22.7 | 11.5 | 9.8 | 9.5 | 10.9 | 64.4 |
| Tohoku | 378 | 36.8 | 11.9 | 6.9 | 9.3 | 12.2 | 77.0 |
| Kanto | 4048 | 48.6 | 11.1 | 7.0 | 8.5 | 7.9 | 83.1 |
| Chubu | 876 | 50.8 | 10.4 | 6.7 | 9.8 | 9.0 | 86.8 |
| Kansai | 1775 | 46.4 | 13.5 | 6.4 | 9.1 | 9.5 | 84.8 |
| Chugoku | 306 | 37.6 | 11.1 | 6.5 | 10.1 | 8.8 | 74.2 |
| Shikoku | 130 | 38.5 | 14.6 | 6.2 | 9.2 | 9.2 | 77.7 |
| Kyushu | 244 | 33.2 | 14.3 | 8.6 | 10.2 | 9.0 | 75.4 |
| | 8105 | 45.7 | 11.7 | 7.0 | 9.0 | 8.8 | 82.1 |

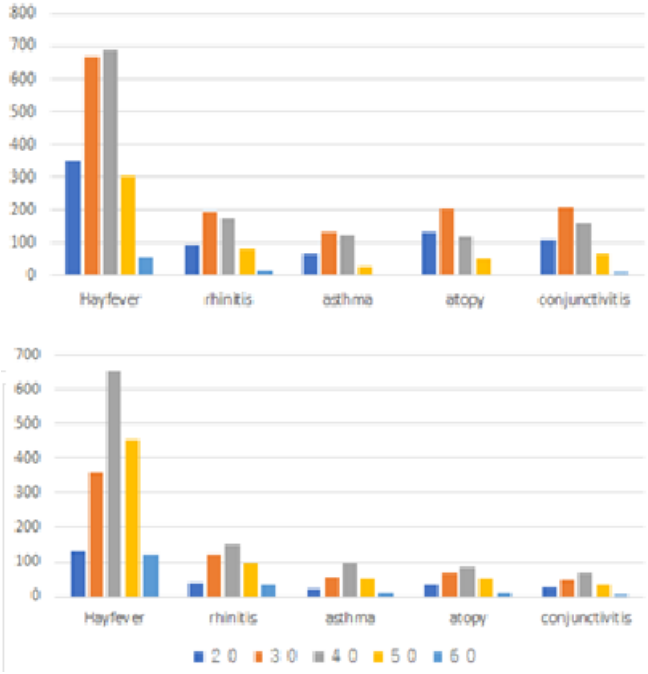


Fig. 2. Number of allergic patients by age category
Upper; Females(n=4452), Lower; Males (n=3884).

In females, the 30s and 40s were high in allergic disease, while the 40s was the highest in males with hay fever.

Hay fever and allergic diseases showed a significant correlation with each other.

The number of multiplicities was shown in Table 2. Hay fever and allergic rhinitis, and allergic conjunctivitis were often complicated. Complication with asthma was the lowest (3.8%).

Table 2. The assortment of allergic diseases

| | n | % |
|---|---|---|
| No allergic symptom | 3367 | 40.4 |
| 1 symptom | 3157 | 37.9 |
| 2 symptoms | 1340 | 16.1 |
| 3 symptoms | 340 | 4.1 |
| 4 symptoms | 102 | 1.2 |
| 5 symptoms | 27 | 0.3 |
| 6 symptoms | 3 | 0 |
| Total | 8336 | 100 |

| | n | % |
|---|---|---|
| Hay fever Yes | 3785 | 45.4 |
| Rhinitis Yes | 990 | 11.9 |
| Asthma Yes | 584 | 7 |
| Atopy Yes | 748 | 9 |
| Conjunctivitis Yes | 733 | 8.8 |
| Others Yes | 578 | 6.9 |
| Total | 7418 | 89.00 |

| | n | % |
|---|---|---|
| Hay+Rhinitis | 618 | 7.4 |
| Hay+Conjunctivitis | 516 | 6.2 |
| Hay+Atopy | 411 | 4.9 |
| Hay+Asthma | 318 | 3.8 |
| Hay+Other | 303 | 3.6 |
| Total | 2166 | 25.90 |

| | n | % |
|---|---|---|
| Hay+Rhinitis + Asthma | 96 | 1.2 |
| Hay+Asthma+Atopy | 85 | 1 |
| Hay+Rhinitis + Conjunctivitis | 143 | 1.7 |
| Total | 324 | 3.9 |

| | n | % |
|---|---|---|
| Hay_Rhinitis_Conjunctivitis_Atopy | 48 | 0.6 |
| Hay_Rhinitis_Conjunctivitis_Atopy_Asthma | 21 | 0.3 |
| Total | 69 | 0.9 |

Table 3. Influenza incidence in each year and number of vaccination

| | Influenza incidence | | | | | |
|---|---|---|---|---|---|---|
| | 2006_7 | % | 2007_8 | % | 2008_9 | % |
| none | 7361 | 88.3 | 7637 | 91.6 | 7648 | 91.7 |
| Atype | 294 | 3.5 | 230 | 2.8 | 331 | 4.0 |
| Btype | 66 | 0.8 | 50 | 0.6 | 59 | 0.7 |
| unknown | 616 | 7.4 | 420 | 5.0 | 299 | 3.6 |
| | 8337 | 100.0 | 8337 | 100.0 | 8337 | 100.0 |
| | Vaccine | | | | | |
| | 2006_7 | % | 2007_8 | % | 2008_9 | % |
| no_vac | 6490 | 77.8 | 6214 | 74.5 | 6076 | 72.9 |
| vac1time | 1753 | 21.0 | 2022 | 24.3 | 2167 | 26.0 |
| vac2time | 94 | 1.1 | 101 | 1.2 | 94 | 1.1 |
| | 8337 | 100.0 | 8337 | 100.0 | 8337 | 100.0 |

The vaccine was a mixed type of anti-influenza A and influenza B

The "vaccine effective rate against influenza disease prevention" was calculated under the presence of hay fever. In the group without hay fever, the effective vaccine rate against influenza disease was 0.2%, and in the hay fever group, it was 0.21%. No effect of the influenza vaccine was found in this population. Rather, vaccination seemed to increase influenza incidence in people with hay fever. (Fig. 3). Actually, in no vaccination group, the incident rate of influenza was 10.6% in the non-hay fever group, while 12.9% in the hay fever group. ($p<0.001$). Hay fever was more susceptible to influenza infection. In the vaccination group, the incidence of influenza rate was 9.78% in the no-hay fever group, while it was 13.89% in the hay fever group. It was shown that the influenza vaccination seemed to suppress a little (9.78% vs. 10.6%) in patients without hay fever, but the basic presence of allergic condition influenza vaccination increased susceptibility to influenza infection. (12.9% vs. 13.89%)($p<0.001$).

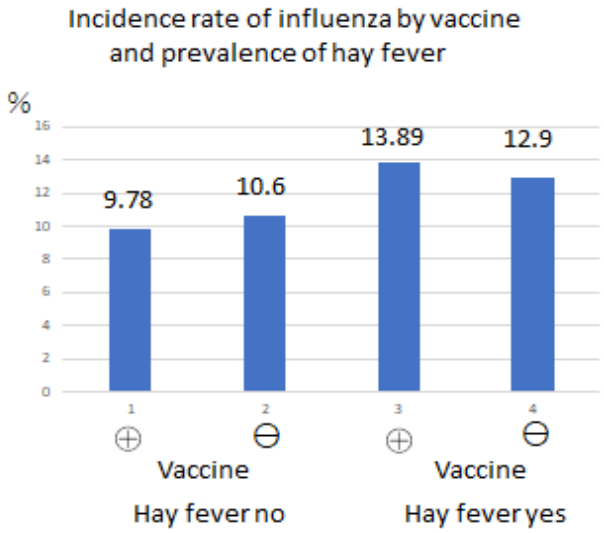


Fig.3. The incidence rate of the influenza by the vaccination and the prevalence of hay fever

As a result, patients with hay fever appear to be more sensitive at protecting against influenza. Infection with the influenza virus was not suppressed by influenza vaccination. The person who received two vaccinations showed a higher correlation with allergic rhinitis and asthma, but the correlation became small in allergic rhinitis.

Discussion

sIgA is the significant component of mucosal immunity, which functions in the gastrointestinal tract and the upper respiratory tract. It constitutes the first line of defense against pathogens by interfering with pathogen adhesion to mucosal cells and promoting pathogen neutralization. [4,12,14] Hay fever is a common disease in

Japan.[15] Although it occurs seasonal, it shows a significant correlation with rhinitis, atopy, asthma, conjunctivitis, and other allergic condition, so the inflammatory state seemed to continue throughout the year. We found patients with hay fever showed low IgA and s-IgA levels. IgA is considered to play an essential role in mucosal infection. So, patients with hay fever may be more sensitive for influenza infection.

Influenza viruses that cause influenza are roughly classified into type A, type B, and type C. Of these, types A and B are the major causes of epidemics in Japan, so vaccine was prepared for both viruses.

Duration of adequate time after vaccination was still under debate.[17] Repeated vaccination was recommended to vulnerable people. In this study, two vaccinations did not show effectiveness.

The influenza vaccine is based on the principle of inoculating by injection to produce a specific IgG antibody against a part of the influenza virus's peptides in the blood to prevent influenza infection. However, the virus infection site is on the upper respiratory tract mucosa, and illness cannot be prevented unless s-IgA had been present. Therefore, it is considered more effective as a vaccine to enhance s-IgA to prevent mucosal infection.[18]

Recently, studies have been conducted to induce s-IgA in the nasal cavity to prevent influenza virus infection.[17]

In humans, Effectiveness of influenza vaccine was determined, "If the risk of getting the disease in people who have not been vaccinated is taken as a standard, "How much has it decreased?" In our study, it was only 0.25%. The current flu vaccine is not that you will never get the flu if you get it. However, it is said to have a certain effect in preventing influenza and preventing severe illness and death after flu.

Keshavarz et al. [19] demonstrated that influenza A- (H1N1) and B-infected patients and also ILI controls have different profiles of immune parameters, and individuals carrying the specific cytokine-derived polymorphisms may show different immune responses towards a severe outcome.

The presence of hay fever and allergy diseases suggested a risk of influenza vaccination probably due to an altered immune state. Until the development of a new type of vaccine shall be established tailor-made strategy for these patients should be necessary for preventing influenza. [20,21]

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